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Roles of white matter in central nervous system pathophysiologies

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ABSTRACT

The phylogenetic enlargement of cerebral cortex culminating in the human brain imposed greater communication needs that have been met by the massive expansion of WM (white matter). Damage to WM alters brain function, and numerous neurological diseases feature WM involvement. In the current review, we discuss the major features of WM, the contributions of WM compromise to brain pathophysiology, and some of the mechanisms mediating WM injury. We will emphasize the newly appreciated importance of neurotransmitter signalling in WM, particularly glutamate and ATP signalling, to understanding both normal and abnormal brain functions. A deeper understanding of the mechanisms leading to WM damage will generate much-needed insights for developing therapies for acute and chronic diseases with WM involvement.

Key words: demyelination, excitotoxicity, human brain, ischaemia, multiple sclerosis, spinal cord injury, stroke.

INTRODUCTION

WM (white matter), as opposed to GM (grey matter), exclusively contains axons and their glial cell partners; absent from WM are neuronal cell bodies, dendrites and conventional synaptic structures. Glial cells in WM are unique. WM astrocytes have especially long, highly discrete processes, which have led to their designation as '*fibrous*' astrocytes (Kettenmann and Ransom, 2005). Oligodendrocytes, which make and sustain myelin, predominate in WM, although their density varies regionally as a function of the percentage of axons that are myelinated in a given tract (e.g. 100% in optic nerve to fewer in corpus callosum). Myelin consists of tightly wrapped oligodendrocytic processes that surround larger diameter axons and mediate saltatory action potential conduction, which increases conduction velocity by at least 50-fold compared with unmyelinated fibres of similar diameter.

WM comprises approximately one-half of the forebrain volume of humans, a 3- to 4-fold increase over rodents, the animals most often used in neuroscience research (Zhang and Sejnowski, 2000; Hamner et al., 2011). The very low relative volume of WM in rodents has contributed to serious misunderstanding regarding the pathophysiology of stroke, and perhaps other diseases, and has slowed progress to effective therapy (Ransom and Baltan, 2009).

WM damage implies primary or secondary disruption of axon function causing disturbance of signal transmission and altered neurological functions that can range from acute, devastating loss of motor function (Hamner et al., 2011) to subtle changes in motor and sensory performance or cognitive impairment (Filley, 2001; Desmond, 2002). The subject is broad and in this review, we focus primarily on mechanisms by which the neurotransmitters glutamate and ATP support WM function in health or cause damage to it under pathological conditions.

NEUROTRANSMITTER SIGNALLING IN WM

Glial cells are endowed with the molecular machinery to communicate with neurons (and among themselves) using neurotransmitters. These mechanisms of cell-to-cell communication are not without controversy (Agulhon et al., 2010; Perea and Araque, 2010), but appear to participate in synaptic transmission and neuronal–glial networking in a manner that contributes to brain function (Verkhratsky,

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Abbreviations: AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmic reticulum; GABA, γ-aminobutyric acid; ERK, extracellular-signal-regulated kinase; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; GluR, glutamate receptor; GluK2, kainate receptor subunit 2; GluT, glutamate transporter; GM, grey matter; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NCX, Na^+/Ca^{2+} exchanger; NG2, nerve/glial antigen 2; NMDA, *N*-methyl-D-aspartate; PVL, periventricular leukomalacia; WM, white matter; xCT, glutamate–cystine exchange transporter.

2010). The signalling capacity of glial cells is not confined to GM. Glia in WM have similar attributes, although in the absence of conventional neuronal synapses their functional significance is less clear (Stys, 2005; Constantinou and Fern, 2009; Butt, 2011; Matute, 2011). Intriguingly, one way that glial cells communicate in WM is a form of signalling that resembles 'classical' synapses between neurons (Kukley et al., 2007; Ziskin et al., 2007; Etxeberria et al., 2010). Adding to this emerging scenario, a new type of chemical synapse between axons and myelin has recently been proposed (Stys, 2011). This section summarizes current knowledge on the mechanisms of WM communication through neurotransmitters emphasizing glutamate and ATP signalling, which has been thoroughly studied in WM. In addition, WM cells are also endowed with an array of GABA (γ-aminobutyric acid)-A, nicotinic, and glycine receptors whose physiological significance remains to be elucidated (Domingues et al., 2010).

Glutamate signalling in glia and axons

Glutamate signalling occurs via GluRs (glutamate receptors) and is terminated by GluTs (glutamate transporters). Glutamate activates ionotropic and metabotropic receptors that are expressed in glial cells in both GM and WM (for recent reviews, see Verkhratsky and Kirchhoff, 2007; Bakiri et al., 2009; Matute, 2011). In particular, cells of the oligodendrocyte lineage express functional AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and kainate type receptors throughout a wide range of developmental stages and species, including humans (Matute et al., 2007a). In addition, immature and mature oligodendrocytes express NMDA (*N*-methyl-D-aspartate) receptors, which can be activated during injury in very young animals (Káradóttir et al. 2005; Salter and Fern, 2005; Micu et al. 2006); the situation in adult animals appears to be more complicated (Baltan et al., 2008). Moreover, oligodendrocytes also express receptors from all three groups of metabotropic GluRs; however, the expression level of these receptors is developmentally regulated and is very low in mature cells of this lineage (Deng et al. 2004).

Glutamate uptake from the extracellular space is conducted by specific GluTs, and is essential for the shaping of excitatory postsynaptic currents and for the prevention of excitotoxic death due to over stimulation of GluRs (Rothstein et al. 1996). At least five GluTs have been cloned (Danbolt, 2001). Of these, GLT-1 (glutamate transporter 1, also known as EAAT2) exhibits the highest level of adult expression, overwhelmingly in astrocytes, and it is responsible for most glutamate transport (Danbolt, 2001). GluTs are also expressed by oligodendrocytes, although their expression has been less well characterized in these cells than in astrocytes. The main transporter expressed by oligodendrocytes is GLAST (glutamate aspartate transporter; also known as EAAT1). The neuronal transporter, termed EAAC1 (excitatory amino acid carrier 1 or EAAT3), is present in a subpopulation of adult oligodendrocyte progenitor cells (Domercq et al. 1999). It appears that all macroglial cells differentially express the three major GluTs present in the CNS (central nervous system). These transporters maintain basal levels of extracellular glutamate in the range of 1–2 μM and prevent over-activation of GluRs under physiological conditions. In turn, GluTs can contribute to glutamate release in WM by reversing Na^+-dependent glutamate transport during depolarization (Domercq et al., 1999; Li et al., 1999; but see Longuemare et al., 1999). While glutamate transport in GM is predominately mediated by astrocytes (e.g. Anderson and Swanson, 2000) there is less information about this function in WM.

In addition, glutamate homoeostasis is also regulated by system x_c^-, a membrane-bound, Cl^--dependent, Na^+-independent antiporter that mediates the cellular uptake of cystine in a 1:1 exchange for glutamate (Conrad and Sato, 2012). The cystine/glutamate antiporter is the main neuronal source of cystine, which is intracellularly converted to cysteine, the rate-limiting substrate in glutathione synthesis. System x_c^- is vital for antioxidant defence; its expression is rapidly up-regulated under oxidative stress, although its enhanced function increases extracellular glutamate levels and may cause excitotoxicity (Conrad and Sato, 2012). Notably, system x_c^- is expressed by astrocytes, and by resting and activated microglia (Domercq et al., 2007; Pampliega et al., 2011; Had-Aissouni 2012).

Axons are also endowed with GluRs and GluTs. Native AMPA receptors in axons are formed by the GluR4 subunit and kainate receptors are composed of at least GluR5 and GluR6 subunits, which in all instances are located in the internodes (Ouardouz et al., 2009a, b). In turn, the major GluT expressed by axons is GLT-1, although significant levels of GLAST are also present (Li et al., 1999). These results must be carefully interpreted because the mere presence of molecules of interest does not guarantee functional or pathophysiological significance. In this regard, our understanding of WM is perhaps a decade behind GM.

Axon AMPA receptors in spinal axons are weakly permeable to Ca^{2+}, the entry of which releases additional Ca^{2+} from the axoplasmic reticulum by opening intracellular Ca^{2+} channels known as ryanodine receptors (Ouardouz et al., 2009a). In contrast, axonal kainate receptors with the GluR5 subunit are coupled to phospholipase C activation (Ouardouz et al., 2009a). In addition, activation of kainate receptors with the GluR6 subunit induces a small amount of Ca^{2+} entry that stimulates NOS (nitric oxide synthase), as well as a local depolarization that activates L-type Ca^{2+} channels, and subsequently ryanodine receptors, in the axoplasmic reticulum (Ouardouz et al., 2009b). The functional significance of these signalling mechanisms by GluRs in axons is unclear, although they may serve to amplify axonal Ca^{2+} signals that appear to be weak because of the limited quantity of cation available in the narrow space (Ouardouz et al., 2009b). Notably, local activation of axonal AMPA/kainate receptors by glutamate released from periaxonal astrocytes may increase the width of action potentials while they travel down axons (Sasaki et al., 2011). In turn, the broadened

action potential triggers larger calcium elevations in presynaptic boutons and facilitates synaptic transmission to postsynaptic neurons (Sasaki et al., 2011). This glial-mediated action potential modification might enable axonal computation through the geometry of axon wiring.

Glutamate signalling in oligodendrocytes is also relevant to myelination. Action potentials travelling along axons can release glutamate in a vesicular manner, which promotes myelin induction by stimulating the formation of cholesterol-rich signalling domains between oligodendrocytes and axons and increasing the local synthesis of major myelin proteins (Wake et al., 2011).

Together, these observations illustrate that WM glia and axons possess all the major components of the molecular machinery for glutamate signalling.

Purinergic signalling in WM glia and axons

The main endogenous agonists of the purinergic system are adenosine and ATP, which activate P_1 and P_2 purinergic receptors respectively. These receptors are widely distributed throughout the CNS, as well as in other organs. The physiological and pathophysiological characteristics of P_1 and P_2 purinergic receptors have been extensively reviewed (Verkhratsky et al., 2009; Burnstock et al., 2011; Matute and Cavaliere, 2011). In this section, we highlight some major properties of P_1 and P_2 receptors in glia that are relevant to both health and CNS disease.

P_1 receptors

Adenosine is a neuromodulator that typically restrains neuronal excitability by acting at P_1 receptors. P_1 adenosine receptors are metabotropic receptors and are classified as A_1, A_{2a}, A_{2b} and A_3 receptors. A_1 and A_3 receptors can inhibit adenylate cyclase or activate phospholipase C, while A_{2a} and A_{2b} receptors activate cAMP production (Fredholm et al., 2001). Extracellular adenosine levels are directly related to the degree of neural activity and to the catabolism of released ATP by ectonucleotidases. In turn, adenosine can also be released (especially in stressful conditions) through bi-directional and non-concentrative nucleoside transporters, whose main function is to remove extracellular adenosine (Malva et al., 2003). Intracellular adenosine levels are largely controlled by adenosine kinase, which is part of a substrate cycle between adenosine and AMP. Small changes in adenosine kinase activity rapidly translate into major changes in adenosine (Boison et al., 2010). This dual role suggests that adenosine acts as a physiological neuromodulator and as a homoeostatic regulator in pathology.

All four adenosine receptors are present in astrocytes. Their activation results in various direct effects, including hyperpolarization, calcium release from internal stores and calcium entry, as well as modulation of the amplitude and/or kinetics of calcium transients initiated by the activation of metabotropic GluRs, muscarinic receptors and P2Y receptors (Verkhratsky et al., 2009). A serious limitation of these functional studies is that they are mostly restricted to *in vitro* cultures of astrocytes and do not provide evidence of the significance of P_1 receptors *in vivo*. On balance, there is now strong evidence that astrocytes play a key role in the control of extracellular adenosine levels (Boison et al., 2010).

Oligodendrocytes and their precursors also express all four types of P_1 receptors, as shown by PCR in culture and in freshly isolated cells (Stevens et al., 2002). Activation of P_1 receptors in oligodendroglia, by direct application of adenosine or by action potentials in nearby neurons, induces transient calcium increase. Interestingly, adenosine acts as a potent neuronal–glial transmitter to inhibit the proliferation of oligodendrocyte precursor cells, stimulate differentiation, and promote myelin formation (Stevens et al., 2002). Thus, adenosine and ATP released from axons mediate axon-to-oligodendrocyte signalling during development (Fields, 2011).

Microglial cells express ectonucleotidase isoforms, as well as all types of adenosine receptors that endow microglia with the capacity to sense released and ambient ATP (Färber and Kettenmann, 2006). Activation of A_1 and A_2 receptors promotes microglial proliferation, while A_3 receptors mediate the phosphorylation of ERK1/2 (extracellular-signal-regulated kinase 1/2). In turn, the activation of A_{2a} receptors in microglia can release neurotrophic factors in neuroprotection and regulate the synthesis of PGE_2 (prostaglandin E_2; Färber and Kettenmann, 2006).

Central axonal conduction may be modulated by adenosine (Sasaki et al., 2011). Specifically, A_1 receptors are present on corpus callosum axons and actively modulate axon physiology by decreasing the compound action potential amplitude (Fern et al., 1994; Swanson et al., 1998). Importantly, blockade of A_1 receptors in axon shafts increases the width of action potentials, an effect that facilitates synaptic transmission to distant postsynaptic neurons (Sasaki et al., 2011).

P_2 receptors

Glial cells also express a heterogeneous repertoire of ATP receptors, including an ample variety of ionotropic (P2X) and metabotropic (P2Y) purinergic receptor subtypes (Verkhratsky et al., 2009; Butt, 2011). ATP-gated P2X channels are formed by $P2X_1$– $P2X_7$ subunits, and are markedly permeable to Ca^{2+}. Activation of $P2X_1$ and $P2X_1$ results in fast, rapidly desensitizing currents. In contrast, $P2X_2$, $P2X_4$ and $P2X_7$ are capable of a conformational change that results in larger pore diameter after prolonged exposure to ATP.

Astrocytes express most of the P2X and P2Y receptor subtypes, whose activation mediates signalling through the astrocytic syncytium (James and Butt, 2002; Fields and Burnstock, 2006). In particular, activation of $P2X_7$ receptors in astrocytes increases $[Ca^{2+}]_i$ and causes the release of purines. Optic nerve astrocytes also express a variety of P2X receptors, which are highly permeable to Ca^{2+}, and P2Y receptors, which mobilize Ca^{2+} from intracellular stores (James and Butt, 2002), as reported in GM astrocytes.

Cells of the oligodendrocyte lineage are also endowed with P2X and P2Y receptors, which can act as mediators of axo-oligodendroglial communication related to myelination control (Fields, 2011). In particular, ATP induces a rise in cytosolic Ca^{2+} in oligodendrocytes by activating ionotropic $P2X_7$ receptors (James and Butt, 2002; Matute et al., 2007b) and metabotropic P2Y receptors (Kirischuk et al., 1995; James and Butt, 2002). Moreover, mature oligodendrocytes of the optic nerve express most of the P2X receptor subtypes, with the $P2X_7$ subtype being the most predominant; it is located in the oligodendrocyte soma and the myelin sheath (James and Butt, 2002; Matute et al., 2007b). P2X receptors with higher affinity may be activated by ATP released during axonal electrical activity and/or from astrocytes (Butt, 2011). In contrast, the functional significance of lower affinity $P2X_7$ receptors in oligodendrocytes is not known, since unusually high ATP concentrations are needed in the extracellular space to activate them. However in pathological conditions, ATP levels may rise sufficiently to stimulate $P2X_7$ receptors upon tissue damage, and therefore they may be relevant to acute and chronic WM injury (Wang et al., 2004; Matute et al., 2007b). Moreover, oligodendrocyte progenitor cells express the uracil nucleotide/cysteinyl leukotriene receptor, which modulates oligodendrocyte differentiation and acts as a sensor for acute and chronic damage (Boda et al., 2011).

Microglia express several P2X and P2Y receptors that act as sensors of astrocyte activity and trigger cytokine release (Fields and Burnstock, 2006; Färber and Kettenmann, 2006). Major subtypes of purinergic receptors expressed by microglia include $P2X_4$, $P2X_7$, $P2Y_6$ and $P2Y_{12}$ receptors (Burnstock et al., 2011). Depending on the amount of ATP released during brain damage, microglia can release factors that favour neuroprotection, such as plasminogen and IL-6 (interleukin-6), or that are detrimental to neuronal survival. In particular, microglial $P2X_7$ receptors drive microglial activation and proliferation (Monif et al., 2009) and are functionally linked to the release of several substances that influence pathological processes and promote neurodegeneration, including pro-inflammatory cytokines such as IL-1β (Färber and Kettenmann, 2006). Moreover, ATP is a potent immunomodulator that controls microglial recruitment and activation (Davalos et al., 2005; Nimmerjahn et al., 2005) by acting at $P2Y_{12}$ receptors to induce microglial chemotaxis at early stages of the response to local CNS injury (Haynes et al., 2006).

Structural and functional properties of WM synapses

The old dogma stated that chemical synaptic specializations occurred exclusively between neurons. This idea was challenged by the discovery of functional glutamatergic and GABAergic synapses between axon terminals and NG2 (nerve/glial antigen 2)-expressing cells in the hippocampus (Bergles et al., 2000; Lin and Bergles, 2004). The character of these NG2-expressing cells has been difficult to elucidate fully. Under certain conditions, they are able to differentiate into oligodendrocytes; however, they also have properties reminiscent of astrocytes. Their function(s), beyond representing a progenitor cell pool for oligodendrocytes, is not understood. NG2 cells in WM also make occasional synapses with unmyelinated axons in an en passant fashion (Kukley et al., 2007; Ziskin et al., 2007; Etxeberria et al., 2010; reviewed in Mangin and Gallo, 2011). Thus, action potentials induce vesicular release of glutamate from unmyelinated axons in the corpus callosum that activate NG2 AMPA receptors during development and in the mature brain. To add to this complex mosaic of glutamate signals, axonal–glial synapses may also be modulated by the vesicular release of glutamate from astrocytes, as observed in classical interneuronal synapses (Volterra and Meldolesi, 2005).

Activation of glutamatergic and GABAergic synapses in NG2 cells induces Ca^{2+} entry directly through the receptor channel or indirectly through the activation of voltage-dependent calcium channels and/or the reversal of NCX (Na^+/Ca^{2+} exchanger) (reviewed by Mangin and Gallo, 2011). Neuron-NG2 synapses are formed during spontaneous remyelination after demyelination, a feature suggesting that they may act in the early steps of the myelination/remyelination process (Etxeberria et al., 2010). This possibility is supported by the fact that NG2 cells lose their synapses as they differentiate into myelinating oligodendrocytes (Kukley et al., 2010). Therefore it is plausible that glutamatergic synapses inhibit NG2 cell proliferation in an activity-dependent manner (Mangin and Gallo, 2011). Indeed, glutamate is known to inhibit NG2 cell proliferation, increase their migration speed, and inhibit their ability to differentiate into oligodendrocytes *in vitro* (reviewed in Mangin and Gallo, 2011).

The axo-myelin synapse

Mature CNS myelin sheaths express various AMPA and kainate receptor subunits, as well as functional NMDA receptors (reviewed in Stys, 2011). Curiously, these NMDA receptors have unique properties: they lack NR2A,B subunits, seem to have NR2C,D instead, and some are NR1/NR3A 'glycine-only' receptors; and they display reduced Ca^{2+} permeability and Mg^{2+} sensitivity. In turn, myelin also expresses purinergic $P2X_7$-type receptors (Matute, 2011). Interestingly, immunogold labelling and electron microscopic examination revealed that both NMDA and $P2X_7$ receptors are preferentially localized at the inner and outer myelin loops.

The presence of neurotransmitter receptors in the inner myelin loop led to the hypothesis that myelin is the target for neurotransmission across a putative axo-myelin synapse, with the internodal axon cylinder acting as the presynaptic element and the periaxonal space equivalent to the synaptic cleft (Stys, 2011). Indeed, vesicular release of transmitter is apparent in unmyelinated axon-to-NG2 cell synapses (see above), and premyelinated central axons contain glutamate-laden vesicles and the machinery for vesicular release (Alix et al., 2008); however, it is unclear whether this mechanism persists after

maturation. In addition, WM possesses neurotransmitter uptake systems in the axon membrane, particularly at the nodes of Ranvier, as well as in the myelin (reviewed in Stys, 2011).

Together, these findings suggest that communication between axons and myelin shares many features of conventional chemical synapses found in GM. This axon–myelin interplay may provide a mechanism by which myelin-supporting oligodendrocytes up-regulate the transfer of energy metabolites to fuel a more electrically active fibre (Stys, 2011). Such a system might seem at odds with evidence that glycogen (which is contained exclusively in astrocytes) supports axons during intense activity or in the temporary absence of glucose. In fact, astrocytes and oligodendrocytes form gap junctions, and may cooperate to provide a 'supply line' for the delivery of energy substrate to axons, whether they are myelinated or not. Although this hypothesis needs further experimental support, it provides novel ideas that may be relevant to myelination and WM damage.

Pathophysiology of neurotransmitter signalling in WM

We have outlined above that WM glia and axons communicate through neurotransmitters in a manner that shares many of the features common to classical chemical synapses. In this section, we will discuss how neurotransmitter signalling, particularly glutamate and/or ATP signalling pathways, may initiate and/or contribute to glial cell death and axonal damage. Then, we will describe current evidence illustrating its relevance to WM pathology in CNS disorders (Table 1). Emerging evidence indicates that nicotinic receptors and adrenoreceptors may also be involved in WM injury (Constantinou and Fern, 2009; Nikolaeva et al., 2009). However, the potential relevance of those findings requires further assessment.

Glutamate excitotoxicity in WM

The term excitotoxicity was coined more than 50 years ago, and refers to neuronal damage by excessive activation of glutamate ionotropic receptors. Although the concept was created to explain GM injury, especially during stroke, it is also highly relevant to WM (Ransom and Baltan, 2009), where receptor-mediated glutamate toxicity is clearly involved in certain pathological conditions.

Over-activation of AMPA and kainate receptors causes oligodendrocyte death and primary and/or secondary myelin destruction (Matute, 2011). The influx of Ca^{2+} upon receptor activation and the ensuing accumulation of Ca^{2+} within mitochondria are central to this process. These events lead to mitochondrial depolarization, increased production of radical oxygen species and the release of pro-apoptotic factors, which in turn activate caspase-dependent and -independent oligodendrocyte death (Sánchez-Gómez et al., 2003). Detailed studies of oligodendrocyte excitotoxicity have shown that Bax and calpain are essential intermediaries (Sánchez-Gómez et al., 2011), and that Ca^{2+}-induced calcium release through ryanodine receptors also contributes to mitochondrial dysfunction and ER (endoplasmic reticulum) stress (Ruiz et al, 2010). However, the mechanisms triggered by NMDA receptor-mediated insults to oligodendrocytes have not yet been studied in detail.

The direct inhibition of glutamate uptake in axonal tracts leads to oligodendroglial loss, massive demyelination, and severe axonal damage (Domercq et al., 2005). Other factors that may contribute to perturbing glutamate homoeostasis and cause WM damage include: altered activity of the glutamate-producing enzyme glutaminase in activated macrophages/microglia in close proximity to dystrophic axons (Werner et al., 2001); and reduced expression of the GluTs, GLAST and GLT-1 in oligodendrocytes as a consequence of enhanced exposure to the pro-inflammatory cytokine TNFα (tumour necrosis factor α) (Pitt et al., 2003) and oxidative stress (Domercq et al., 2007). Moreover, activated microglia increase their own expression of xCT (glutamate–cystine exchange transporter), which contributes further to increasing glutamate levels and glutamate toxicity (Domercq et al., 2007). In turn, excessive activation of internodal axonal GluRs may induce the release of substantial amounts of calcium from axoplasmic ER and activate calcium-dependent enzymes that ultimately ignite the collapse of the axon (Stirling and Stys, 2010).

ATP excitotoxicity in WM

Purinergic signalling is relevant to neuroinflammation associated with neurodegenerative diseases. These pathologies give rise to increased levels of extracellular adenine nucleotides which, through the activation of a variety of cell surface P_2 purinergic receptors, influence the inflammatory activities of responding immune cells. In particular, the $P2X_7$ receptor potentiates the release of pro-inflammatory cytokines (such as IL-1β) from microglia and induces cell death. In addition, ATP originating from dying cells may act as part of a secondary mechanism to aggravate the extent of ongoing CNS damage. Accordingly, neuroprotective properties of classical and novel selective and non-selective $P2X_7$ receptor antagonists have been observed in various cellular and animal models of CNS disorders to which excessive inflammatory activities contribute (reviewed in Friedle et al., 2010).

Similar to GM, WM is vulnerable to excessive ATP signalling. Excess ATP is a potent endogenous toxin that can directly kill oligodendrocytes by activating $P2X_7$ receptors (Matute et al., 2007b). ATP excitotoxicity in oligodendrocytes is Ca^{2+}-dependent and induces cell death by apoptosis or necrosis, depending on the intensity of the insult. In addition, $P2X_7$ receptor engagement activates several second messenger and enzyme cascades. In macrophages/monocytes and microglia, $P2X_7$ receptor stimulation rapidly activates JNKs (c-Jun N-terminal kinases) 1 and 2, ERKs and p38 MAPK (mitogen-activated protein kinase) (reviewed in Skaper et al., 2010). Transcription factors whose activation and nuclear

Table 1 **White matter damage and dysfunction in CNS disorders and their animal models**
EAE, experimental autoimmune encephalomyelitis; GluK2, kainate receptor subunit 2; KO, knockout; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; nAChR, nicotinic acetylcholine receptor; OPC, oligodendrocyte precursor cell.

Disease	Model/preparation	Target/finding	Mechanism	References
Stroke	Optic nerve	NCX	Blockade is protective	Stys et al. (1992)
	Cultured oligodendrocytes	AMPA/kainate receptors	Blockade prevents oligodendro toxicity	Fern and Möller (2000)
	Neonatal isolated optic nerve	NMDA receptors	Blockade prevents oligodendro toxicity	Káradottir et al. (2005), Salter and Fern (2005) and Micu et al. (2006)
	Older optic nerve	AMPA/kainate receptors NMDA receptors	Blockade is protective Blockade is NOT protective	Baltan et al. (2008)
	Oligodendrocytes and optic nerve	$P2X_7$/pannexin-1	Receptor/hemichannel blockade	Domercq et al. (2010)
	MCAO	A2A receptors	Blockade prevents oligodendro-toxicity	Melani et al. (2009)
Perinatal ischaemia	Hypoxia–ischaemia	AMPA and NMDA receptors	Blockade prevents oligodendro-toxicity	Follett et al. (2004) and Manning et al. (2008)
	Immature optic nerve	AMPA and NMDA receptors	Blockade prevents axon damage	Alix and Fern (2009)
	Hypoxia–ischaemia plus LPS	Axon-OPC synapses	Reduced oxidative stress	Shen et al. (2012)
	Hypoxia–ischaemia	$P2X_7$ receptors	Blockade prevents oligodendro-toxicity	Wang et al. (2009)
	A1 receptor KO	A1 receptors	Reduced WM damage	Turner et al. (2003)
Multiple sclerosis	Acute and chronic EAE	AMPA receptors	Blockade protects myelin and axons	Pitt et al. (2000), Smith et al. (2000) and Kanwar et al. (2004)
	Microglia activation in optic nerve	AMPA/kainate receptors	Blockade prevents oligodendro-toxicity	Domercq et al. (2007)
		xCT	Blockade prevents oligodendro-toxicity	
	Oligodendrocytes and optic nerve	Kainate receptors	Blockade prevents complement attack	Alberdi et al. (2006)
	Chronic EAE in GluK2 KO	GluK2	Reduced symptoms and damage	Pérez-Samartín et al. (2009)
	Chronic EAE	$P2X_7$ receptors	Blockade attenuates symptoms and damage	Matute et al. (2007b)
	Human brain imaging	Glutamate	Altered homoeostais	Srinivasan et al. (2005)
Spinal cord injury	Dorsal columns	AMPA/kainate receptors	Blockade attenuates damage	Li and Stys (2000)
	Contusion	$P2X_7$ receptors	Blockade preserves function	Peng et al. (2009)
	Crush	GLT-1	Lower expression increases damage	Lepore et al. (2012)
AD	Postmortem human brain	Oligodendrocyte apoptosis	Unknown	Bronge (2002)
	Imaging of human brain	WM	Oxidative stress damage	Back et al. (2011)
	Cultured oligodendrocytes	Unknown	β-amyloid oligotoxicity	Xu et al. (2001)
	Triple transgenic model	Myelin alterations	Unknown	Desai et al. (2009)
Psychiatric disorders	Postmortem brain schizo-phrenia.	Reduction in oligodendrocytes	Unknown	Uranova et al. (2004)
	Schizophrenia and bipolar disorder	Reduced size of WM tracts	Unknown	McIntosh et al. (2008) and Peters et al. (2010)
Unknown	Optic nerve	Adrenoreceptors and nAChR	Action potential block and glial injury	Constantinou and Fern (2009) and Nikolaeva et al. (2009)

translocation are associated with the expression of inflammatory genes [e.g. NF-κB (nuclear factor κB), NFAT (nuclear factor of activated T-cells), CREB (cAMP-response-element-binding protein) and AP-1 (activator protein 1)] are also activated by $P2X_7$ receptors in microglia. Moreover, stimulation of $P2X_7$ receptors involves Ca^{2+} signalling and increases protein tyrosine phosphorylation, ultimately leading to MAPK pathway activation (reviewed in Skaper et al., 2010).

Stroke

Damage of central WM is a major cause of functional disability in cerebrovascular disease; the majority of ischaemic strokes involve both WM and GM (Goldberg and Ransom, 2003; Hamner et al., 2011). Injury to WM as a consequence of hypoxic-ischaemic injury occurs in PVL (periventricular leukomalacia) in neonates and in stroke and cardiac arrest in adults, as well as in vascular dementia in the aging brain. The

metabolic rate of WM is only modestly lower than that of GM, and animal studies suggest that WM can be damaged by even brief ischaemia (Pantoni et al., 1996). Ischaemic insults typically result in transmembrane ion gradient breakdown and membrane depolarization, leading ultimately to toxic intracellular Ca^{2+} overload. The final stage is the activation of Ca^{2+}-dependent enzymes (e.g. calpains, phospholipases and other enzymes), resulting in irreversible damage of WM glia and axons (Stys et al., 1992; Stys, 2004; Hamner et al., 2011). These steps are surprisingly complex and much remains to be learned.

Immature and differentiated oligodendrocytes, studied *in vitro*, are very sensitive to transient oxygen and glucose deprivation (Fern and Möller, 2000). Both cell types can be partially protected from irreversible ischaemic injury by reducing extracellular Ca^{2+} or by AMPA/kainate receptor antagonists, but not by the blockade of other potential sources of Ca^{2+} influx, which suggests that Ca^{2+} entry through the receptor channel is sufficient to initiate cell demise. Notably, simulated ischaemia induces an inward current in oligodendrocytes that is partly mediated by NMDA and AMPA/kainate receptors (Káradóttir et al., 2005). In addition, Ca^{2+} levels also increase in myelin itself during ischaemia (an effect that is abolished by broad-spectrum NMDA receptor antagonists), causing ultrastructural damage to both axon cylinders and myelin (Micu et al., 2006). Unfortunately, WM ischaemic injury in older animals proceeds according to different rules. WM becomes intrinsically more vulnerable to ischaemia in older animals as the mechanisms of injury change as a function of age (Baltan et al., 2008). The removal of extracellular Ca^{2+} or blockade of Ca^{2+} entry by reversing the NCX improves WM function in young animals, but not in older animals (Baltan et al., 2008). Indeed, Ca^{2+}-free conditions worsen recovery from ischaemic insult in older animals, suggesting that Ca^{2+} release from intracellular Ca^{2+} stores may become more critical during ischaemia in aging WM. In turn, ischaemic WM injury in older mice is predominately mediated by glutamate release through reverse glutamate transport (probably from astrocytes) and the ensuing activation of AMPA/kainate-type GluRs (Baltan et al., 2008). Intriguingly, blockade of NMDA receptors aggravates the outcome of ischaemia in older animals (Baltan et al., 2008).

These findings clearly indicate that the mechanisms of ischaemic damage to WM involve Ca^{2+} dyshomoeostasis induced by excessive glutamate signalling, which is age-dependent. This important finding has profound consequences for the development of optimized age-specific therapies for the treatment of brain damage after stroke.

Intracellular levels of ATP decline and extracellular ATP is elevated in GM (WM has yet to be evaluated) during cerebral ischaemia as a consequence of secondary anoxic depolarization (Frenguelli et al., 2007). ATP can be exocytosed in a Ca^{2+}-dependent manner from synaptic vesicles, gap junction hemichannels formed by connexins and pannexins, and other ion channels (e.g. $P2X_7$ receptors; Verkhratsky et al., 2009). In turn, ischaemic insults can open pannexin hemichannels and contribute to ATP release and post-anoxic depolarization in cultured neurons (Thompson et al., 2006), as well as in oligodendrocytes *in vitro* and *in situ* (Domercq et al., 2010), although the results in neurons have not been confirmed in acute slices (Madry et al., 2010). The rise in the extracellular concentration of ATP during ischaemia is sufficient to activate $P2X_7$ receptors and kill neurons and oligodendrocytes, an event that is prevented by blockade of $P2X_7$ receptors (Domercq et al., 2010; Arbeloa et al. 2012). In oligodendrocytes, in particular, ischaemia triggers an inward current and cytosolic Ca^{2+} overload, which are partially mediated by $P2X_7$ receptors (Domercq et al., 2010). $P2X_7$ receptors in oligodendrocytes are activated, at least in part, by ATP released through the opening of pannexin channels during oxygen and glucose deprivation. This process leads to mitochondrial depolarization and oxidative stress culminating in oligodendrocytic death, which is attenuated by $P2X_7$ receptor antagonists, by the ATP-degrading enzyme apyrase, and by blockers of pannexin hemichannels (Domercq et al., 2010). These data indicate that ATP is released during ischaemia, and that subsequent activation of the $P2X_7$ receptor is critical to WM demise during stroke and in PVL.

Massive release of ATP during transient brain ischaemia (and its subsequent degradation by ectonucleotidases) would result in an increase in adenosine levels that may be sufficient to activate P_1 receptors and may have deleterious effects on the CNS (Burnstock et al., 2011). The blockade of A_{2a} receptors protects from ischaemic damage to oligodendrocytes by reducing the activation of JNK p38 MAPK (Melani et al., 2009). By contrast, adenosine can also be protective, acting through a PKC (protein kinase C) pathway to provide a form of autoprotection (Fern et al., 1994).

Perinatal ischaemia

PVL is the major neuropathological lesion in premature infants, and involves focal WM necrosis and subsequent hypomyelination. Its pathophysiology is multifactorial and includes hypoxia–ischaemia-induced glutamate excitotoxicity, oxidative stress and inflammation (Volpe, 2009). Injury to oligodendrocyte progenitors caused in part by glutamate contributes to the pathogenesis of myelination disturbances in PVL (Back and Rivkees, 2004). In the immature human brain, the susceptibility of developing oligodendrocytes to hypoxia–ischaemia correlates with their expression of GluRs of the AMPA receptor subtypes in the immature human brain (Talos et al., 2006), and systemic administration of AMPA receptor antagonists attenuates injury in a rat model of PVL (Follett et al., 2004). In addition, developing oligodendrocytes also express NMDA receptors; their blockade with memantine attenuates oligodendrocyte loss and prevents the long-term reduction in cerebral mantle thickness that is observed in experimental PVL (Manning et al., 2008). Intriguingly, synapses between axons and oligodendroglial precursor cells are quickly and profoundly damaged in PVL models, an

observation that outlines the relevance of these synaptic contacts to WM integrity during development (Shen et al., 2012).

Ischaemic injury to axons is also a feature of PVL; it occurs early in local and diffuse damage associated with this pathology (Haynes et al, 2008). Interestingly, experimental ischaemia in immature axons produces action potential failure and focal breakdown of the axolemma of small premyelinated axons at sites of contact with oligodendrocytic processes, which are also disrupted (Alix and Fern, 2009). Axon damage is prevented by NMDA and AMPA/kainate receptor blockers, suggesting that GluR-mediated injury to oligodendrocytic processes in contact with premyelinated axons precedes disruption of the underlying axon (Alix and Fern, 2009).

Perinatal ischaemia also triggers lethal activation of $P2X_7$ receptors in oligodendrocyte precursors (Wang et al, 2009). The oligodendrocyte precursors express $P2X_7$ receptors; the levels of these receptors are reduced after oxygen–glucose deprivation *in vitro* and neonatal hypoxic–ischaemic injury, suggesting a role for this receptor in the pathophysiology of hypoxic–ischaemic brain injury (Wang et al, 2009). In addition, A_1 receptors may mediate some of the deleterious effects of perinatal ischaemia on myelin and WM (Turner et al., 2003).

Multiple sclerosis, a hallmark of WM damage

The major demyelinating disease of the CNS is multiple sclerosis, which is the foremost disabling pathology among young adults. Multiple sclerosis is a chronic, degenerative disease of the CNS, which is characterized by focal lesions with inflammation, demyelination, infiltration of immune cells, oligodendroglial death and axonal degeneration (Prineas et al, 2002). It is widely accepted that the aetiology of this illness has autoimmune and inflammatory grounds, and that a derailment of the immune system leads to cell- and antibody-mediated attacks on myelin.

Both genetic and environmental factors contribute to multiple sclerosis susceptibility (Zamvil and Steinman, 2003). Among them, primary and/or secondary alterations in glutamate signalling cause excitotoxicity, which in turn contributes to multiple sclerosis pathology. Numerous studies conducted in cellular and animal models of multiple sclerosis, as well as in post-mortem brain and in patients, have indicated that excitotoxicity mediated by Ca^{2+}-permeable GluRs contributes to oligodendrocyte death, demyelination and tissue damage in multiple sclerosis (Matute et al., 2001; Srinivasan et al., 2005; Vallejo-Illarramendi et al., 2006). In particular, EAE (experimental autoimmune encephalomyelitis), a mouse disease model that exhibits the clinical and pathological features of multiple sclerosis, is alleviated by AMPA and kainate receptor antagonists (Pitt et al., 2000; Smith et al., 2000). Indeed, mice deficient in the GluK2 (kainate receptor subunit 2) are less susceptible to EAE (Pérez-Samartín et al., 2009). Remarkably, blockade of these receptors in combination with anti-inflammatory agents is effective even at an advanced stage of unremitting EAE, as assessed by increased oligodendrocyte survival and remyelination, and corresponding decreased paralysis, inflammation, CNS apoptosis and axonal damage (Kanwar et al. 2004). Importantly, a recent genome-wide association screening study identified associated alleles in AMPA receptor genes in multiple sclerosis patients who exhibited the highest levels of glutamate and brain volume loss (Baranzini et al., 2010). These findings provided a novel quantitative endophenotype that may help clarify the pathophysiology of the heterogeneity of clinical expression in multiple sclerosis. In addition, another component of the genetic background linking multiple sclerosis and the deregulation of glutamate signalling may lie in a polymorphism in the Ca^{2+}-permeable AMPA receptor subunit GluR3 (a subunit that is abundantly expressed in oligodendrocytes), which is associated with a subgroup of patients responding to IFNβ (interferon β) therapy in multiple sclerosis (Comabella et al., 2009). In contrast, blockade of NMDA receptors with MK-801 does not attenuate EAE symptoms (Matute, 2010), a finding that calls into question the proposed relevance of NMDA receptors in demyelinating diseases (Bakiri et al., 2009).

Glutamate levels are increased in the human brain (Srinivasan et al., 2005) as a consequence of reduced expression of the GluTs, GLAST and GLT-1 (Vallejo-Illarramendi et al., 2006). Another mechanism accounting for glutamate dyshomoeostasis is genetic variability in the promoter of the major GluTs, GLT-1, which results in lower transporter expression (Pampliega et al., 2008). In turn, up-regulation of xCT in the monocyte–macrophage–microglia lineage is associated with immune activation in both multiple sclerosis and EAE (Pampliega et al., 2011).

Non-toxic glutamate concentrations also contribute to demyelinating pathology by inducing oligodendrocyte death by sensitizing oligodendrocytes to complement attack (Alberdi et al., 2006). Intriguingly, complement toxicity is induced by the activation of kainate, but not of AMPA, NMDA or metabotropic GluRs. Oligodendrocytic death by complement requires the formation of the membrane attack complex, which in turn increases membrane conductance and induces Ca^{2+} overload and mitochondrial depolarization, as well as an increase in the level of ROS (reactive oxygen species; Alberdi et al., 2006). Sensitization by glutamate to complement attack may initiate multiple sclerosis lesions with massive oligodendrocyte apoptosis, as described earlier (Barnett and Prineas, 2004).

As mentioned above, ATP signalling can trigger oligodendrocyte excitotoxicity through the activation of Ca^{2+}-permeable $P2X_7$ purinergic receptors expressed by these cells. Importantly, sustained activation of $P2X_7$ receptors *in vivo* causes lesions that are reminiscent of the major features of multiple sclerosis plaques, and treatment of chronic EAE with $P2X_7$ antagonists reduces demyelination and ameliorates the associated neurological symptoms (Matute et al., 2007b). These results are in agreement with data in $P2X_7$ null mice showing that this

deficiency suppresses the development of EAE (Sharp et al., 2008), and at odds with earlier observations indicating that the lack of $P2X_7$ receptors aggravates EAE (Chen and Brosnan, 2006), as well as our own unpublished data (A. Pérez-Samartín and C. Matute). These apparent discrepancies may be caused by the different strains and knockout mice used, and to solve this issue will require the development of conditional $P2X_7$ receptor knockout mice that lack this transcript in specific glial cell populations. In turn, the availability of these technical resources would overcome the problem of interfering with the immune system whereby $P2X_7$ receptors may be relevant intermediaries of the response to myelin antigens in EAE. In addition, $P2X_7$ RNA and protein levels are elevated in normal-appearing axon tracts in multiple sclerosis patients, suggesting that oligodendroglial signalling through $P2X_7$ receptors is enhanced in multiple sclerosis, which may render this cell type more vulnerable to ATP dysregulation (Matute et al., 2007b). The increased expression of $P2X_7$ receptors in axon tracts before lesions are formed indicates that this feature may constitute a risk factor associated with newly forming lesions in multiple sclerosis; therefore this receptor subunit may prove to be a diagnostic and/or prognostic clinical biomarker for multiple sclerosis. In addition, blockade of ATP $P2X_7$ receptors protects oligodendrocytes from dying; this property has therapeutic potential to halt the progression of tissue damage in multiple sclerosis.

Other alterations of purinergic signalling in multiple sclerosis include reduced expression of $P2Y_{12}$ receptors in the periphery of demyelinated lesions and increased expression of uracil nucleotide/cysteinyl leukotriene receptor, a P2Y-like receptor that is associated with defective myelination during postnatal life (for review, see Burnstock et al., 2011).

Spinal cord injury

Traumatic injury to the CNS inevitably involves damage to WM and causes primary mechanical destruction of glia and axons. In addition, secondary impairment of tissue occurs as a consequence of a prolonged pathological response involving chronic inflammation, microglial activation and astroglial scar formation. This prolonged response can ultimately result in the development of a large cavity at the site of the lesion and persistent functional deficits (Dumont et al., 2001).

Tissue destruction after traumatic brain injury leads to the release of large amounts of glutamate, which cause Ca^{2+}-dependent excitotoxic damage to WM astrocytes, oligodendrocytes and myelin, but not to axons (Li and Stys, 2000). Indeed, glutamate dysregulation is centrally involved in the outcome following traumatic spinal cord injury. After thoracic crush of the spinal cord, mice heterozygous for the astrocytic GluTs, GLT-1 exhibit attenuated recovery of hind limb motor function, increased lesion size and reduced tissue sparing (Lepore et al., 2012). These findings indicate that glutamate uptake by astrocytes limits secondary damage after CNS traumatic injury, and that promoting GluT expression and function may favour post-lesion recovery.

Furthermore, ATP (which is also present at high levels in the extracellular space after cell death) may cause Ca^{2+}-dependent gliotoxicity, either directly by activating P2X receptors, or after degradation to adenosine and subsequent activation of P_1 purinergic receptors (Verkhratsky et al, 2009). However, the putative deleterious effects of P_1 activation on WM have not yet been demonstrated to occur after traumatic injury.

Finally, spinal cord injury is associated with prolonged $P2X_7$ receptor activation and ensuing neuronal excitotoxicity (Wang et al., 2004). Strikingly, systemic administration of a $P2X_7$ antagonist that is able to cross the blood–brain barrier ameliorates the motor behaviour of animals that had previously been subjected to spinal cord contusion, indicating that neuroprotection after injury can preserve function (Peng et al., 2009). Oligodendrocyte preservation by $P2X_7$ receptor blockade in those experimental conditions may also be critical to attenuate WM destruction and the ensuing motor and sensory deficits.

AD (Alzheimer's disease)

WM is altered in the aging brain, in AD as well as other dementias (Back et al., 2011). A high percentage of AD patients exhibit evidence of WM degeneration, as indicated by severe apoptotic loss of oligodendrocytes (Bronge, 2002) and free radical injury to myelin and axons (Back et al., 2011). It is unclear whether this neuropathological feature is primary or secondary to ongoing neuronal death. However, it may be directly caused by the overload of β-amyloid peptides characteristic of the AD brain, since these peptides damage oligodendrocytes *in vitro* (Xu et al., 2001) and increase their vulnerability to glutamate excitotoxicity (Pak et al., 2003). In turn, injection of β-amyloid (1–42) into WM causes axon disruption and myelin damage, as well as oligodendrocyte loss and profound gliosis (Jantaratnotai et al., 2003).

Transgenic models of AD also point to specific alterations in WM. Mice expressing presenilin-1 mutants are more susceptible to oligodendrocyte excitotoxicity and to demyelinating agents, which result in learning and memory deficits (Pak et al., 2003). These findings reveal that a specific presenilin-1 mutation in oligodendrocytes can have detrimental effects leading to disease, and indicate that WM damage may well contribute to cognitive dysfunction in AD. In addition, triple-transgenic mice harbouring the human Swedish mutant transgene of the amyloid precursor protein, a presenilin knock-in mutation, and a tau P301L mutant transgene, exhibit significant region-specific alterations in myelination and in oligodendrocyte marker expression profiles at time points preceding the appearance of amyloid and tau pathology (Desai et al., 2009). These findings in animal models of AD suggest that myelin and oligodendrocyte defects in AD precede the onset of symptoms and may be key players in the development of this disease.

WM dysfunction in psychiatric diseases

WM alterations have recently been detected in studies of post-mortem brain tissue from psychiatric patients diagnosed with schizophrenia, bipolar disorder and major depression. Although these diseases are distinct in nature, they share some WM distortions that may contribute to their pathophysiology, including reduced oligodendrocyte number and expression of myelin constituents (for recent reviews, see Matute, 2010; Stys, 2011).

Neuropathological studies have revealed myelin defects and oligodendrocyte alterations in brain tissue from schizophrenic patients, correlating with the decreased expression of myelin-related genes (McIntosh et al., 2005). For instance, histological studies have demonstrated an abnormal distribution and decreased density of oligodendrocytes in the frontal regions of the cerebral cortex in schizophrenic patients, as well as reduced cell numbers in certain cortical layers (Uranova et al., 2004). The nature of the mechanisms leading to hypomyelination and reduction of the oligodendrocyte population is unknown; however, it has been proposed that hypomyelination may be caused by alterations in Ca^{2+} homoeostasis due to aberrant glutamate signalling in these insidious diseases (Davis et al., 2003). Interestingly, lithium (which is widely used to treat bipolar disorder) regulates a number of components of signal transduction machinery, including Ca^{2+} homoeostasis, and has neuroprotective properties in experimental paradigms of excitotoxicity (Bauer et al., 2003). Finally, diffusion tensor imaging suggests that some axonal tracts are reduced in size, suggesting vulnerable brain areas (McIntosh et al., 2008; Peters et al., 2010) that may underlie changes in action potential propagation caused by myelination pathways relevant to psychiatric diseases (Whitford et al., 2010).

CONCLUSIONS

Primary and/or secondary WM damage occurs in acute and chronic CNS diseases. Oligodendrocytes (the major cell type in WM), the myelin sheath they elaborate and maintain and axons are highly vulnerable to insults that initiate within the CNS or in the immune system, such as multiple sclerosis. The mechanisms triggering WM injury are only partially understood. Oligodendrocytes are particularly sensitive to alterations of glutamate and ATP homoeostasis, which may kill these cells by excitotoxicity through over-activation of both ionotropic GluRs and $P2X_7$ purinoceptors. In addition, it is conceivable that axons, which express AMPA and kainate receptors, may undergo direct glutamate excitotoxicity. The proper functioning of glutamate uptake is critical to prevent glutamate-induced damage to WM, and drugs that regulate the function and expression of GluTs have the potential to attenuate glutamate insults. On the other hand, the control of ATP release and degradation during acute and chronic inflammation, as well as at early stages of post-ischaemic and post-traumatic injury, may prove therapeutic. In addition, other neurotransmitters, including acetylcholine and noradrenaline, can also be harmful to WM and consequently relevant to disease (for a review, see Domingues et al, 2010).

A deeper knowledge about the mechanisms leading to WM injury or demise mediated by glutamate and ATP receptors, and by other neurotransmitters, will facilitate new pharmacological strategies to treat CNS disorders in which WM is severely compromised.

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